HOW SIDE REACTIONS CAN INFLUENCE POLY(2-OXAZOLINE) SYNTHESIS FOR POLYMER THERAPEUTICS AND HYDROGELS

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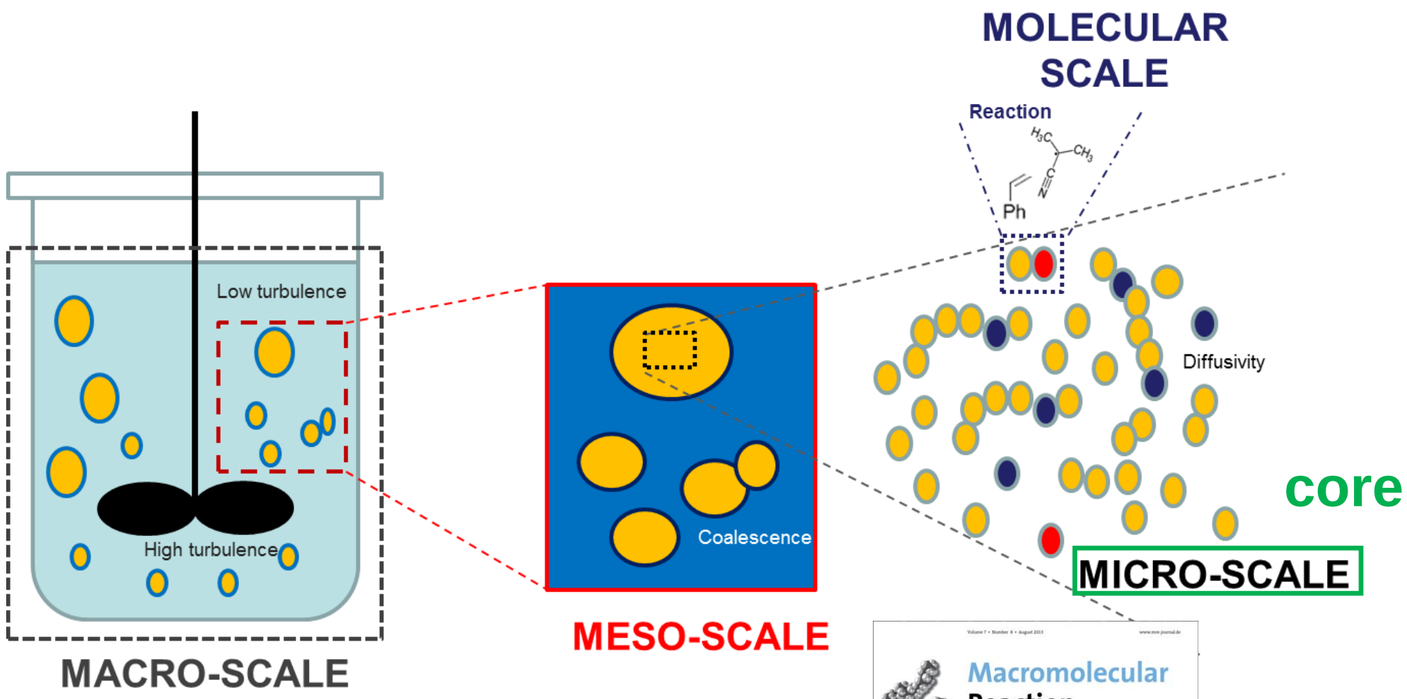
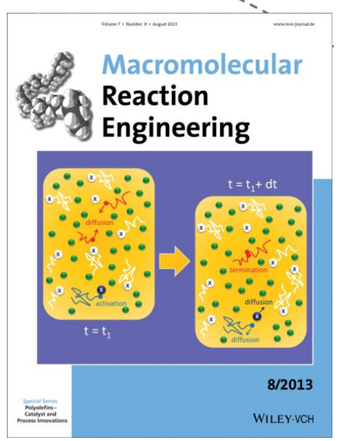
[3]Centre for Textile Science and Engineering (CTSE), Ghent University

MULTI-SCALE CHARACTER OF POLYMERIZATION



D'hooge D.R. *et al. Prog. Polym. Sci.* **2016** 58, 59

Mastan *et al. Prog. Polym. Sci.* **2015**, 45, 71

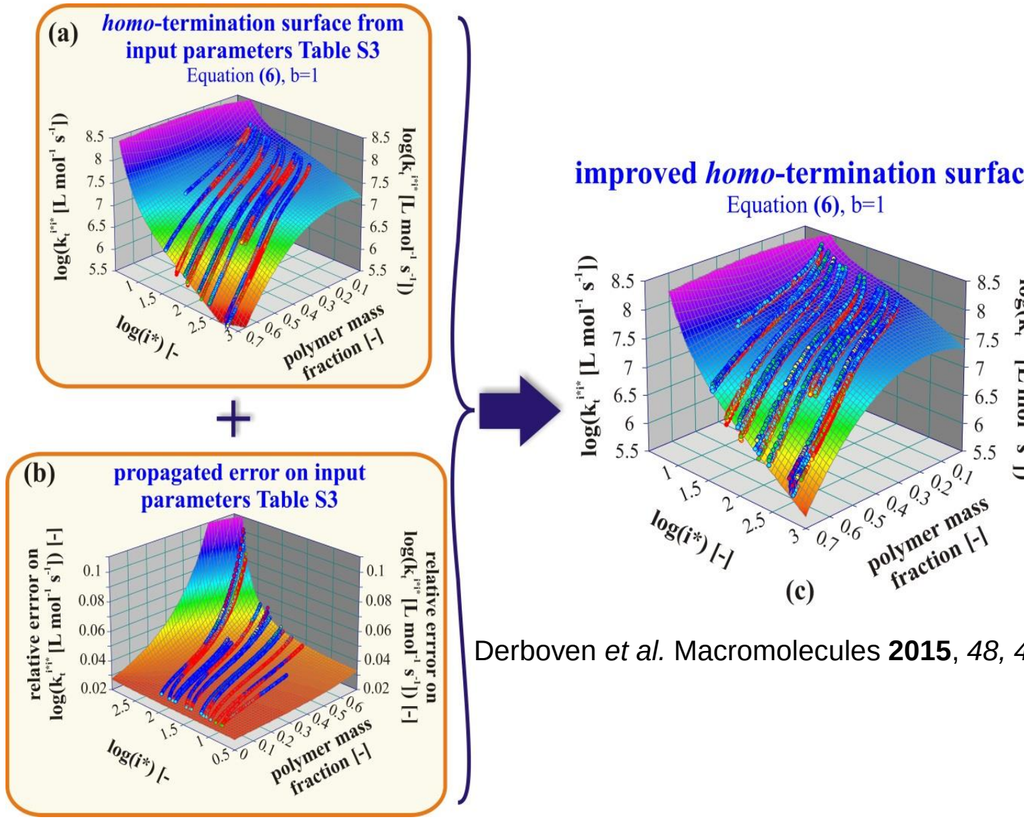


D'hooge *et al.* Macromol. React Eng. **2013**, *7, 362*

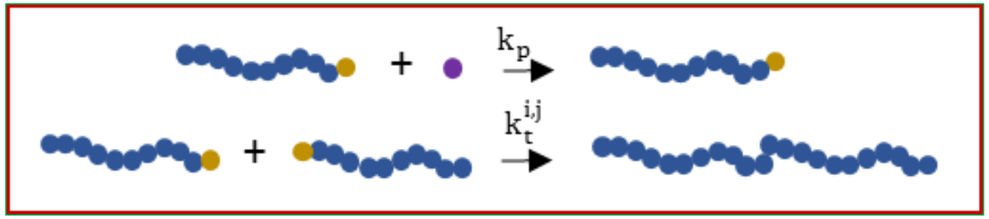
Peklak et al. J. Polym. Sc. Polym Chem/ **2006**, 44, 1071

Achilias and Kiparissides Macromolecules **1992**, *25, 3739*

$$A + B \underset{k_{-diff}}{\overset{k_{+diff}}{\rightleftharpoons}} AB \xrightarrow{k_{chem}} C \quad \Leftrightarrow \quad A + B \xrightarrow{k_{app}} C$$

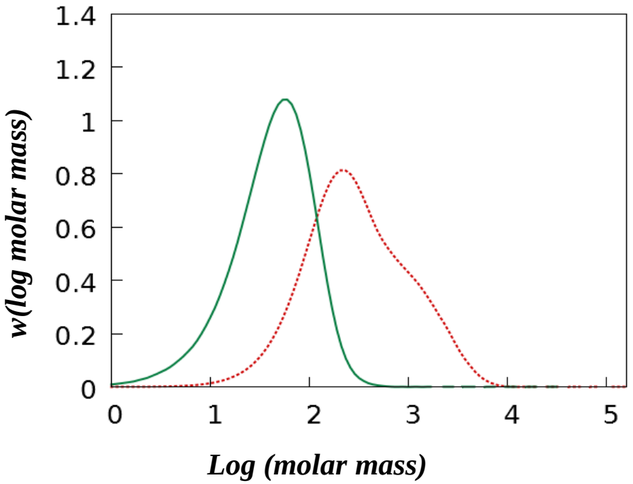


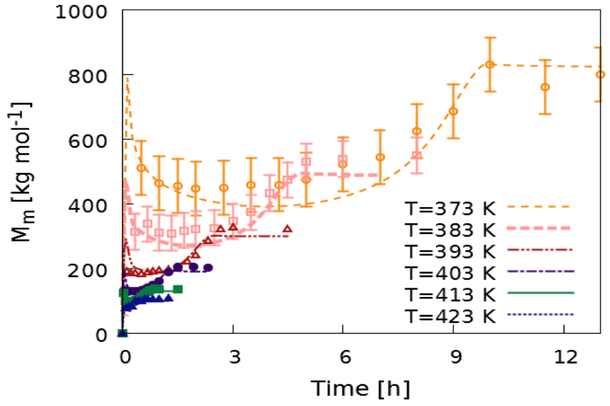
Derboven *et al.* Macromolecules **2015**, *48, 492*



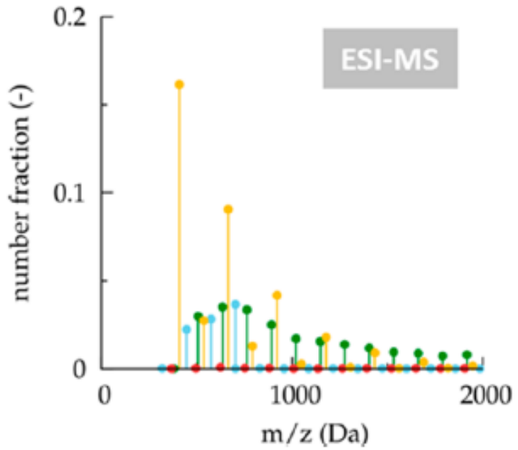
MICRO-SCALE: SYNERGY MODEL AND EXPERIMENT

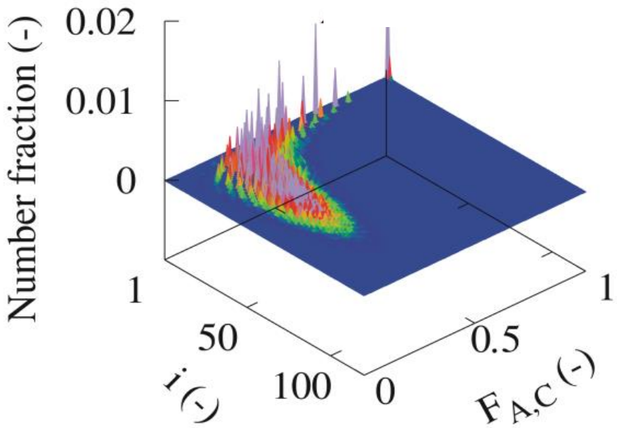
Generation 1



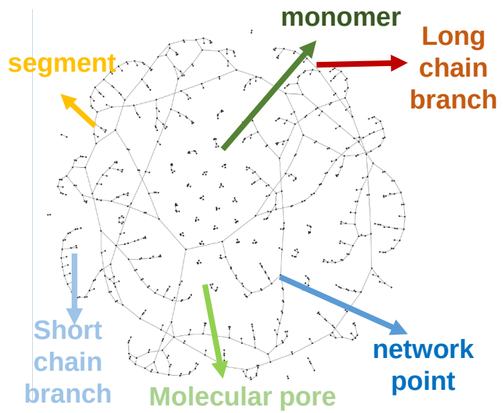


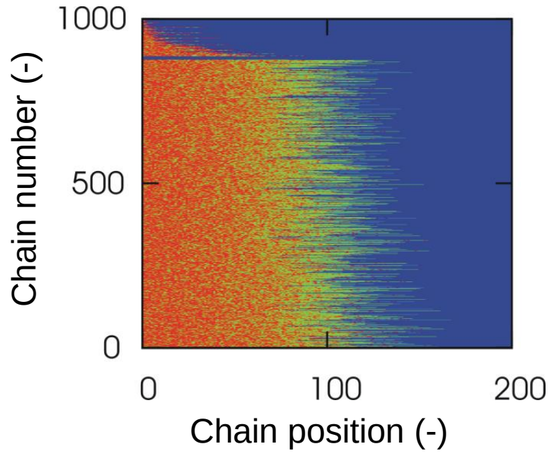
Generation 2



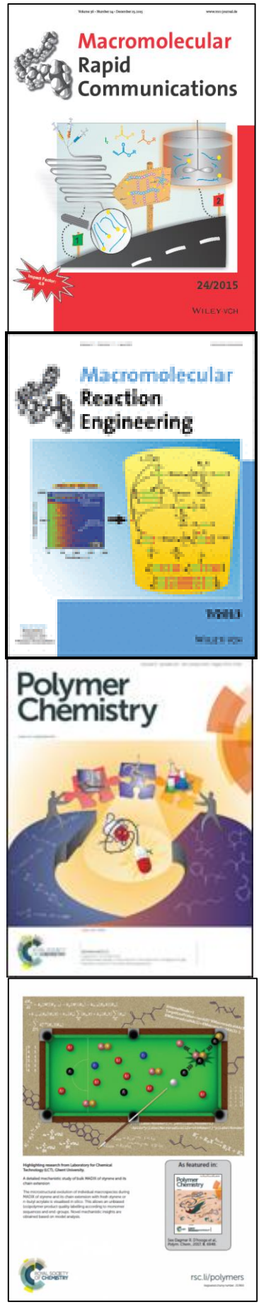


Generation 3





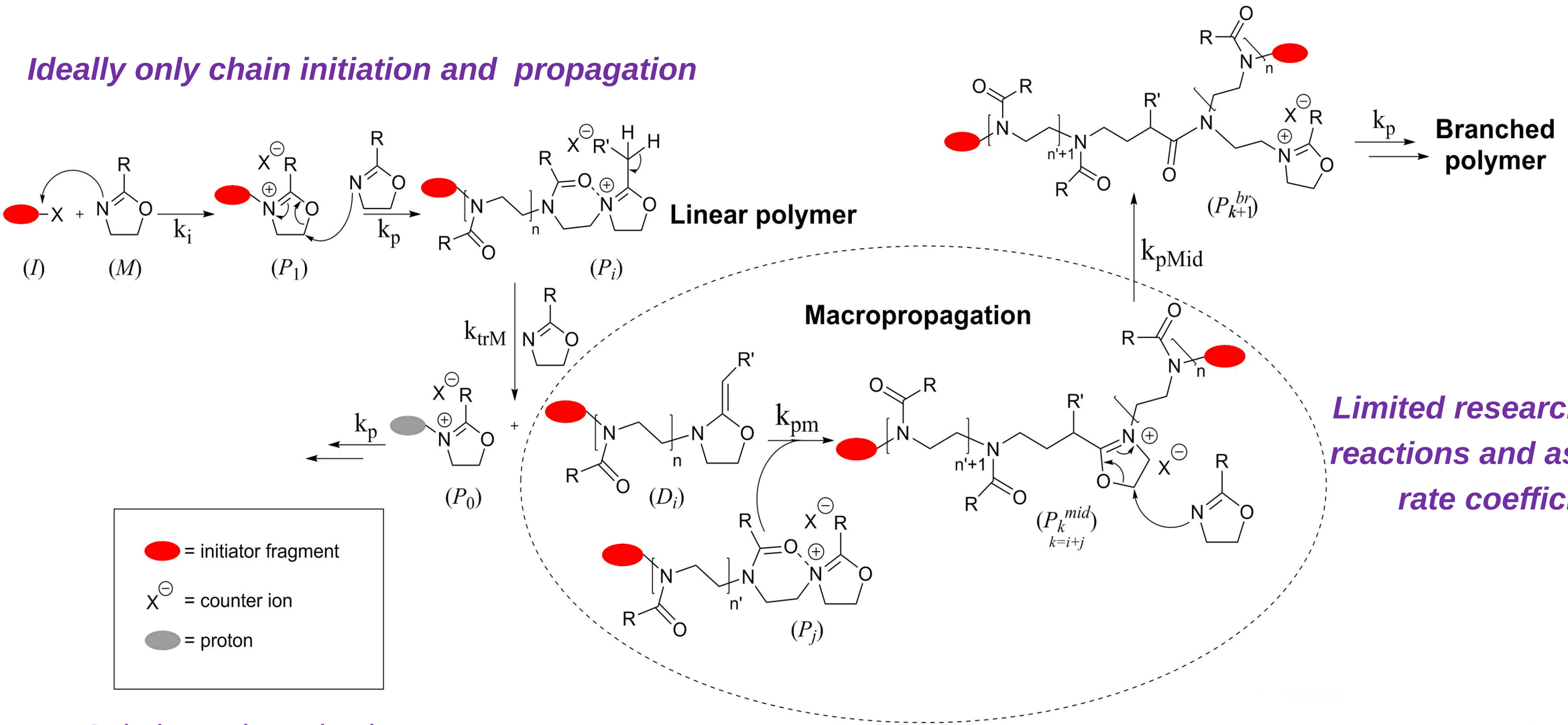
Complexity and macromolecular structural detail



Van Steenberge P.H.M. *et al. Macromolecules* **2011**, 44, 8716; Van Steenberge P.H.M. *et al. Macromolecules* **2012**, 45, 8519.; Van Steenberge P.H.M. *et al. Chem. Eng. Sci.* 2014, 11, 185; D'hooge D.R. *et al. Polym. Chem.* **2015**, 6, 7081; Derboven P. *et al. Macromol. Rapid Commun.* **2015**, 36, 2149; D'hooge D.R. *et al. Prog. Polym. Sci.* **2016**, 58, 59; Devlaminck D.J.G. *et al. Polym. Chem*. **2017**, 8, 6948

CATIONIC RING-OPENING POLYMERIZATION OF 2-OXAZOLINES

Ideally only chain initiation and propagation



Limited research on side reactions and associated rate coefficients

Solution polymerization

Main focus on chemistry

block:

gradient:

=

OUTLINE

1. Homopolymerization

- Chain initiation and propagation reactivity
- Chain transfer to monomer reactivity
- Macropropagation reactivity

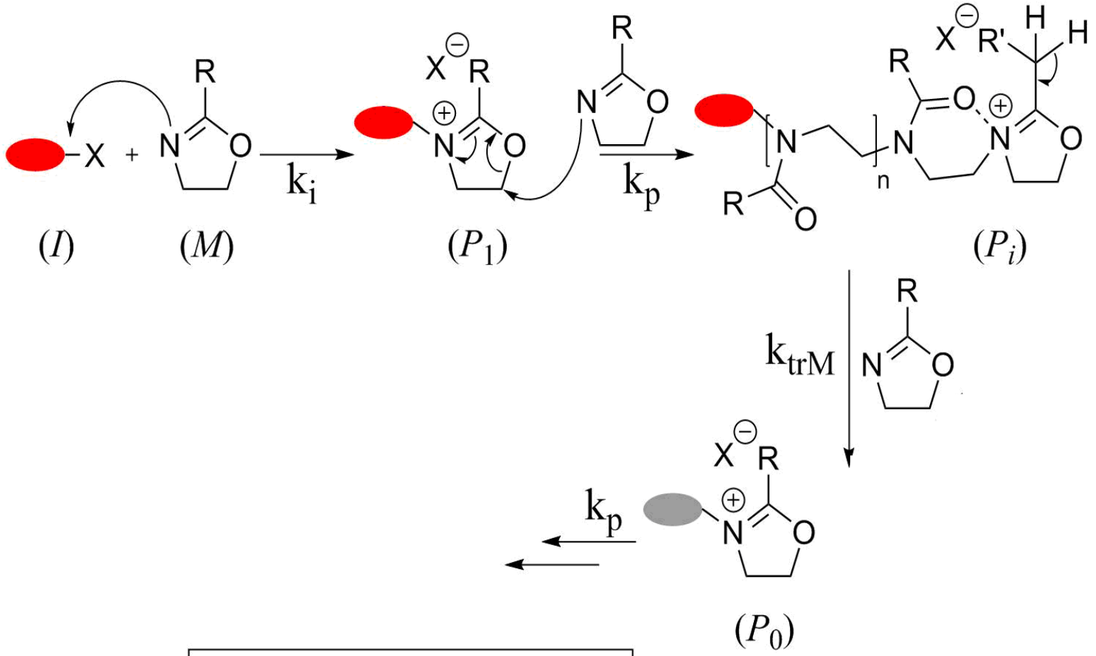
Van Steenberge *et al*. *Macromolecules* **2015**, 48, 7765
Glassner *et al. Eur. Polym. J.*, **2015**, 65, 298
Van Steenberge *et al*. Submitted **2019**.
Arraez *et al*. *Macromolecules* **2019**, accepted.

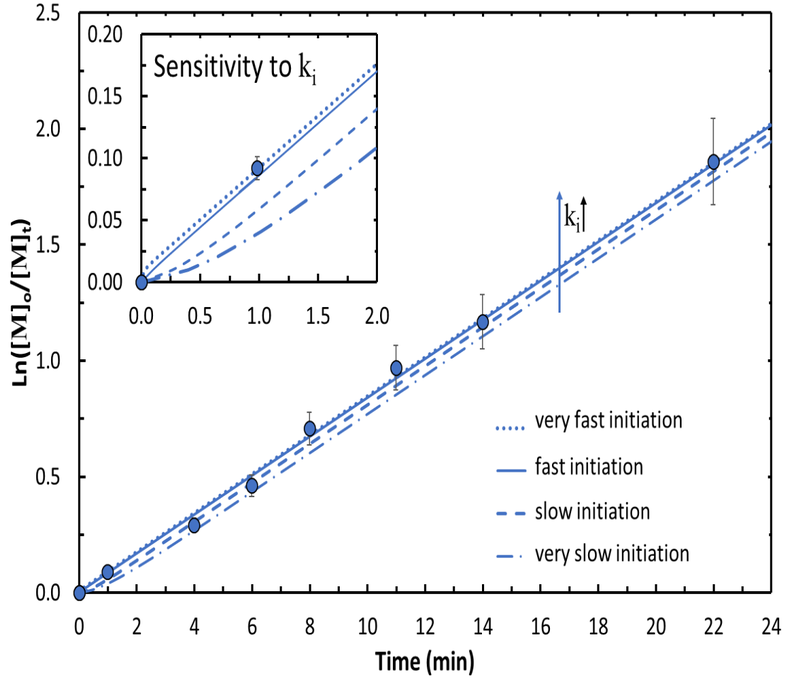
2. Copolymerization with functional comonomer in view of therapeutics & hydrogels

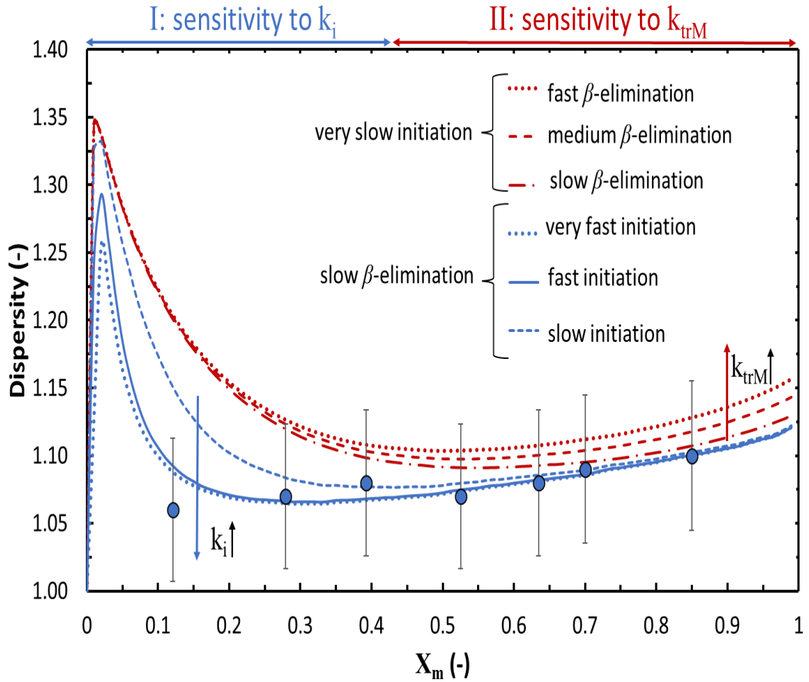
- Unbiased qualification tool for evaluation functionalization success
- Design of chemical structure of the comonomers and reaction conditions
- Applicability for low and high target degrees of polymerization (target DPs)

Van Steenberge *et al*. *Macromolecules* **2015**, 48, 7765
Van Steenberge *et al*. Submitted **2019**..

WHICH EXPERIMENTAL RESPONSES ?







CROP of EtOx ($[M]_o$ = 4 mol·L^{-1}; target DP of 100; acetonitrile; 393 K

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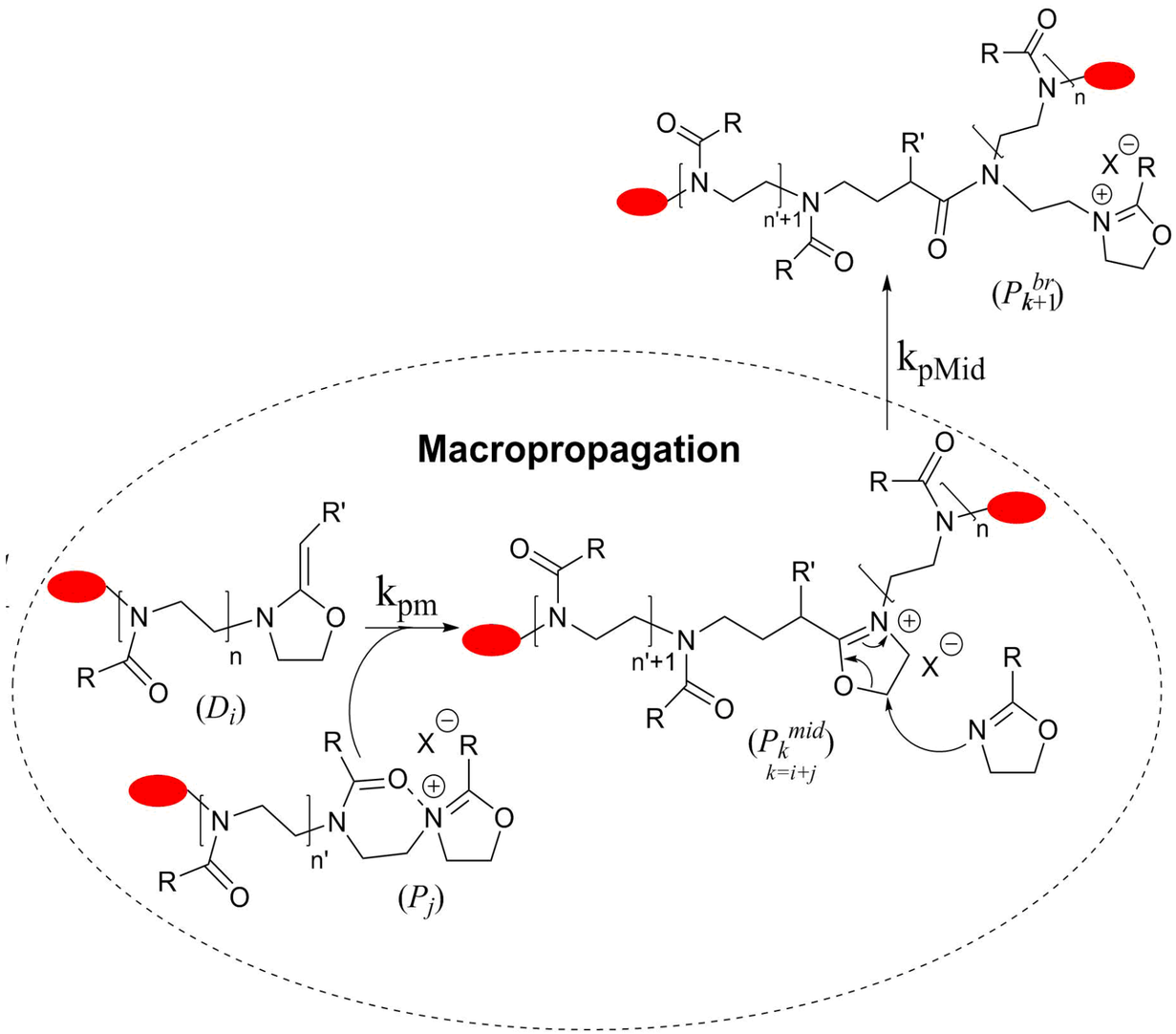
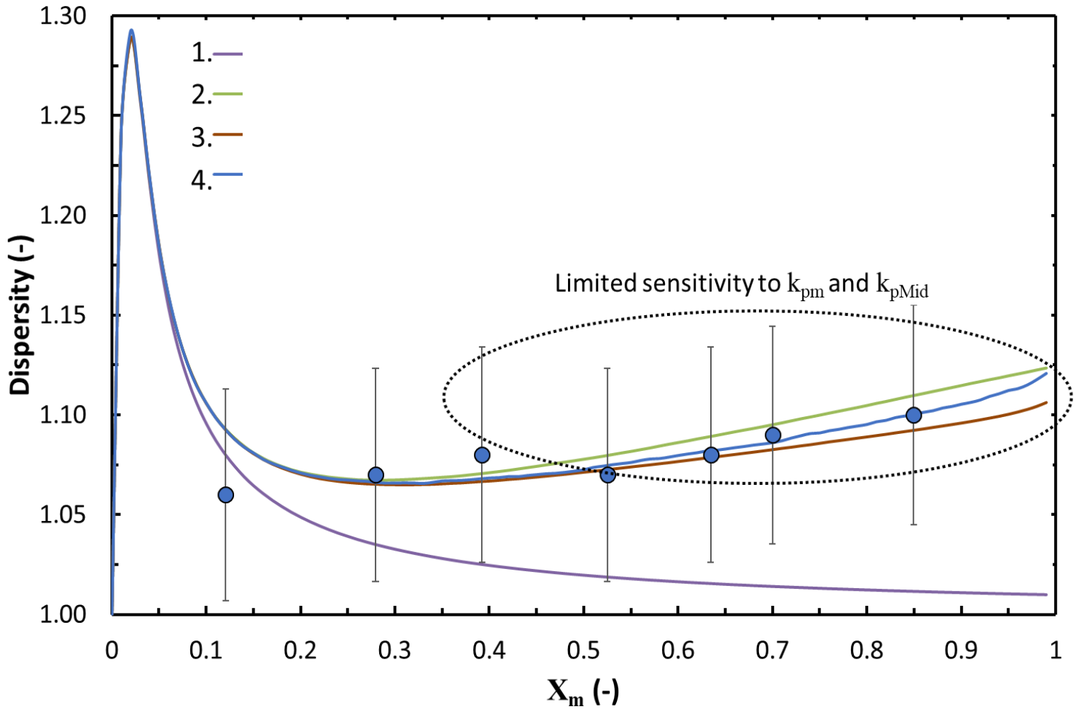


	k_{trM} (L·mol^{-1}·s^{-1})	k_{pm} (L·mol^{-1}·s^{-1})	k_{pMid} (L·mol^{-1}·s^{-1})
1.	✖	✖	✖
2.	✓ 6.57×10^{-2}	✖	✖
3.	✓ 6.57×10^{-2}	✓ 6.99×10^{-2}	✖
4.	✓ 6.57×10^{-2}	✓ 6.99×10^{-2} ×0.1	✓ 3.49×10^{-2}
5.	✓ 6.57×10^{-2}	✓ 6.99×10^{-3}	✓ 3.49×10^{-2} ×10
6.	✓ 6.57×10^{-2}	✓ 6.99×10^{-3}	✓ 3.49×10^{-1}
● ---		Experimental	



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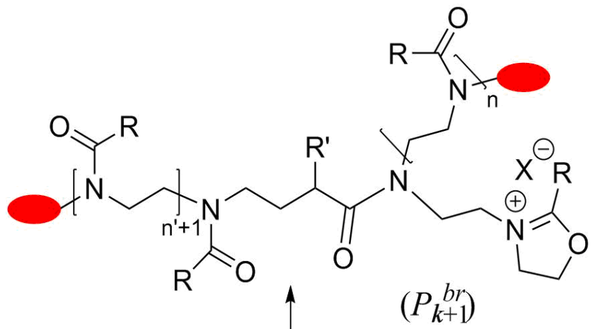
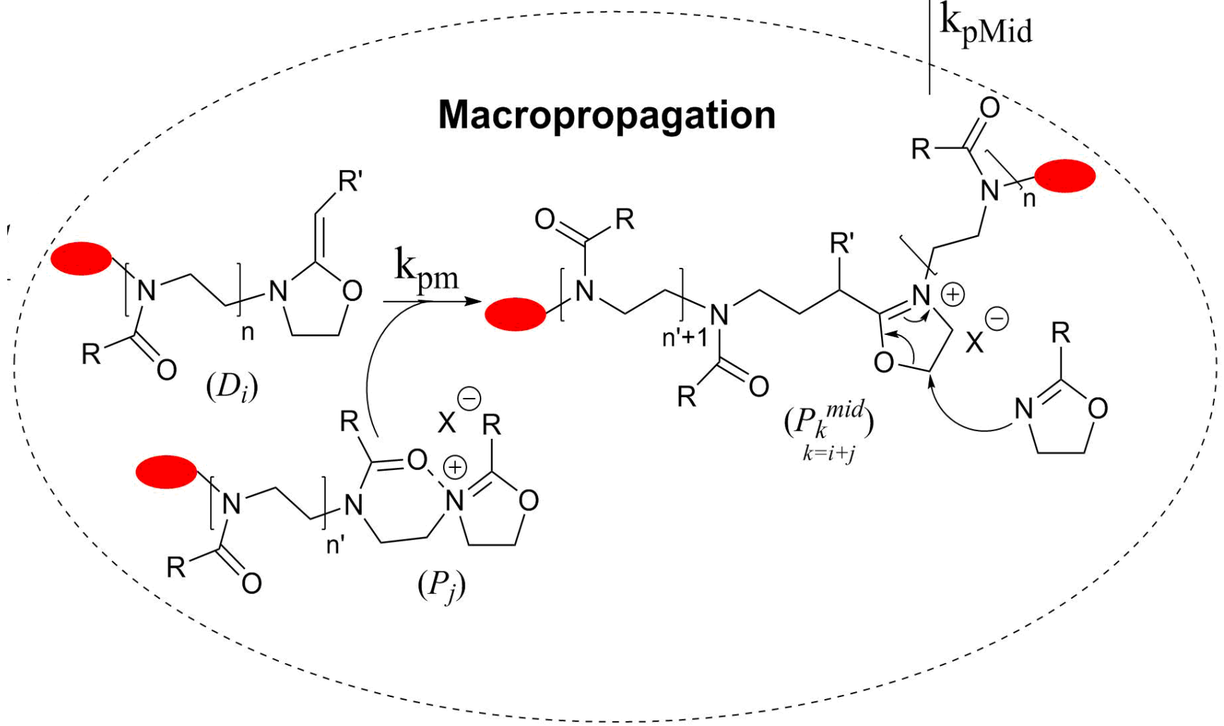
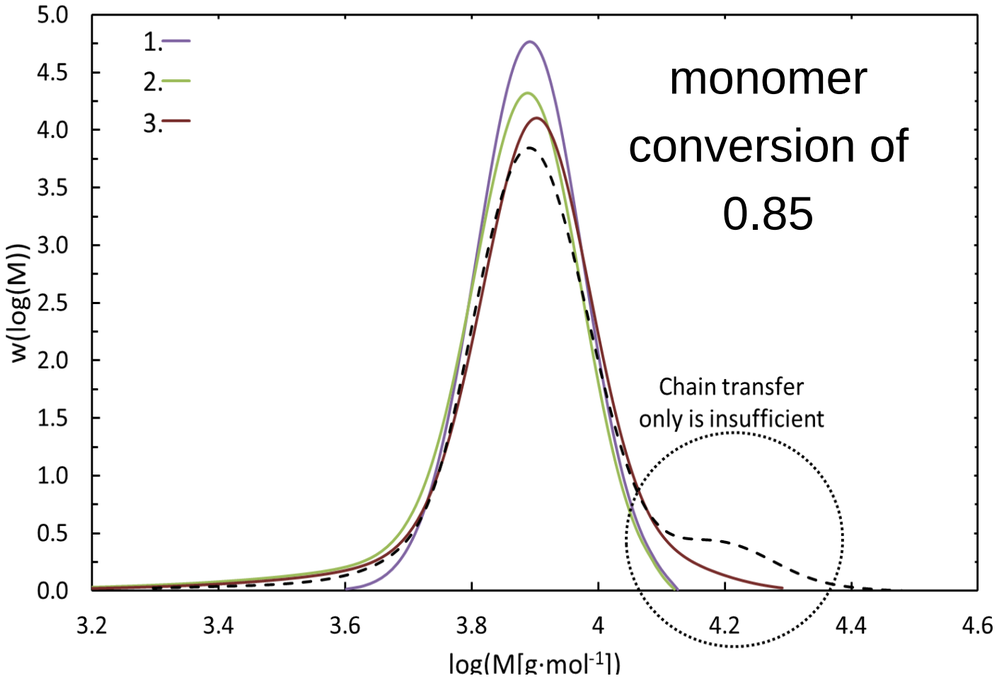
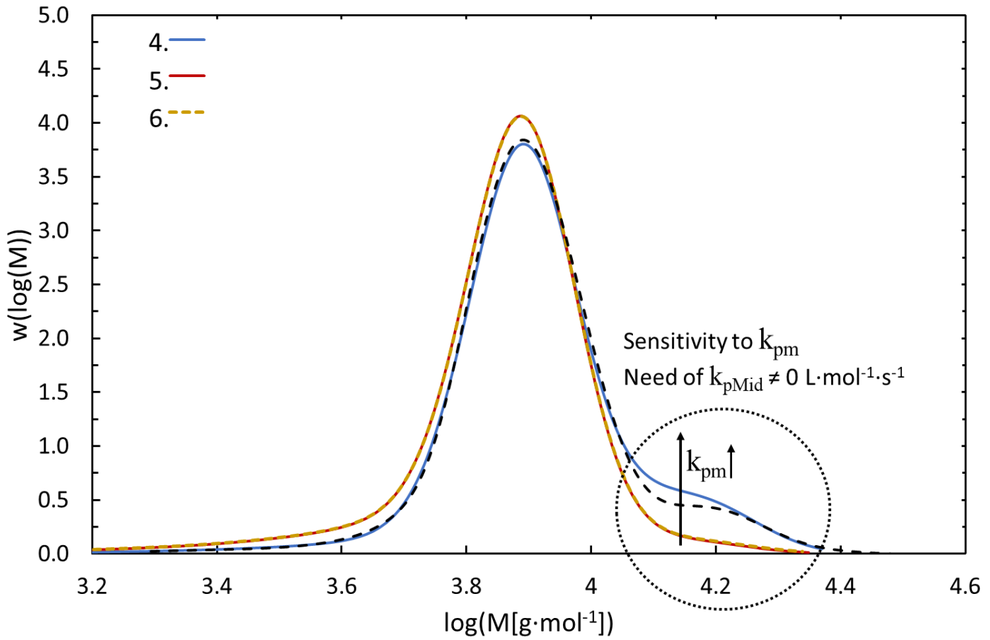
WHICH EXPERIMENTAL RESPONSES ?

	k_{trM} (L·mol^{-1}·s^{-1})	k_{pm} (L·mol^{-1}·s^{-1})	k_{pMid} (L·mol^{-1}·s^{-1})
1.	✗	✗	✗
2.	✓ 6.57×10^{-2}	✗	✗
3.	✓ 6.57×10^{-2}	✓ 6.99×10^{-2}	✗
4.	✓ 6.57×10^{-2}	✓ 6.99×10^{-2}	✓ 3.49×10^{-2}
5.	✓ 6.57×10^{-2}	✓ 6.99×10^{-3} (×0.1)	✓ 3.49×10^{-2}
6.	✓ 6.57×10^{-2}	✓ 6.99×10^{-3}	✓ 3.49×10^{-1} (×10)
		Experimental	





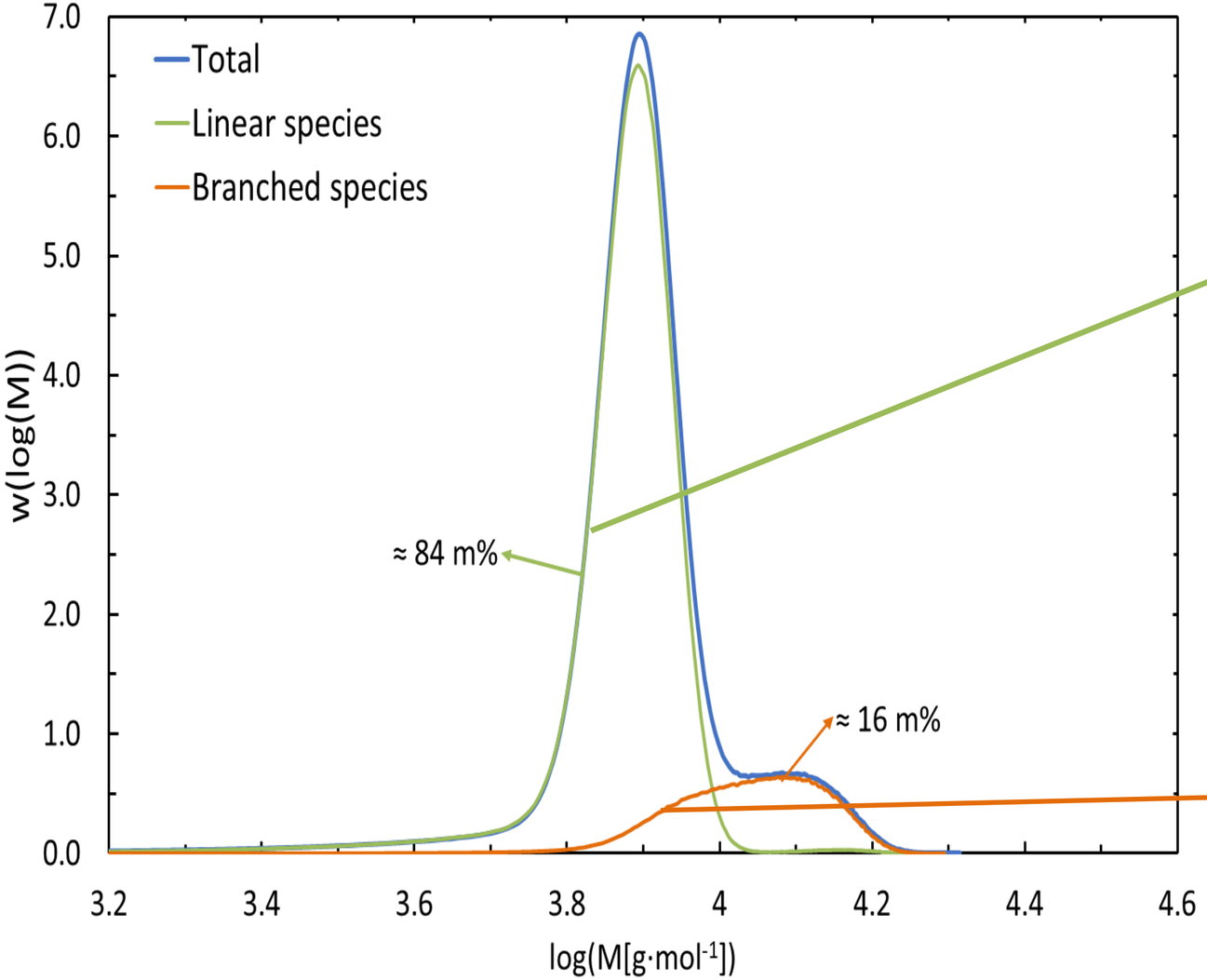


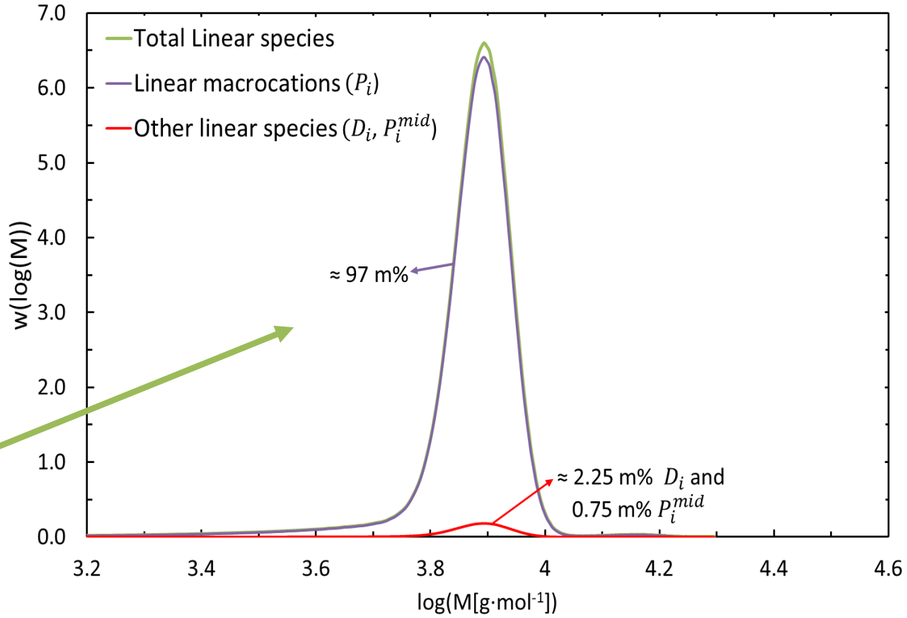


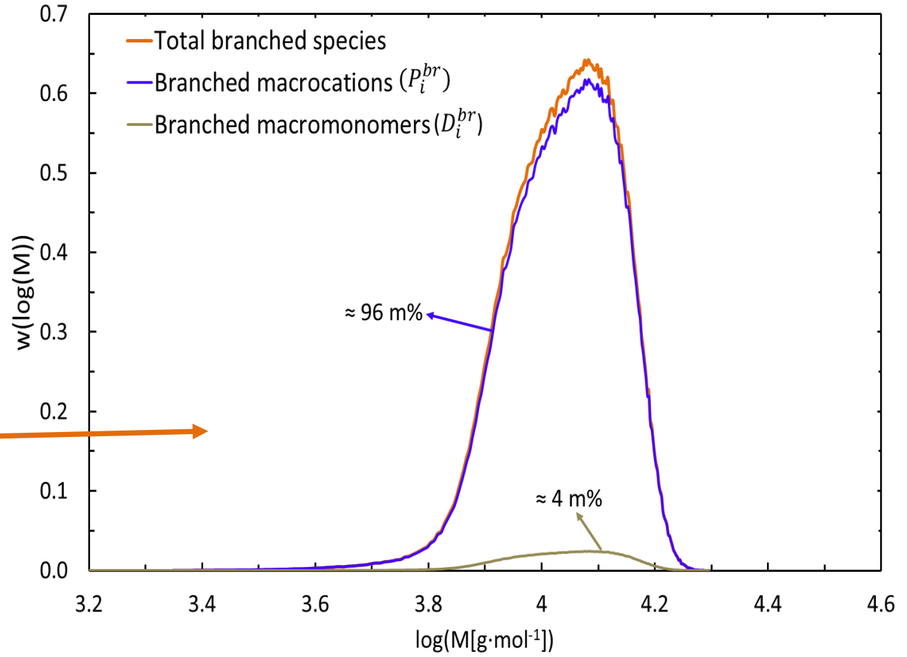
Correction for SEC broadening and topology difference

EXTRA INFORMATION BY MODELING

Differentiation according to topology

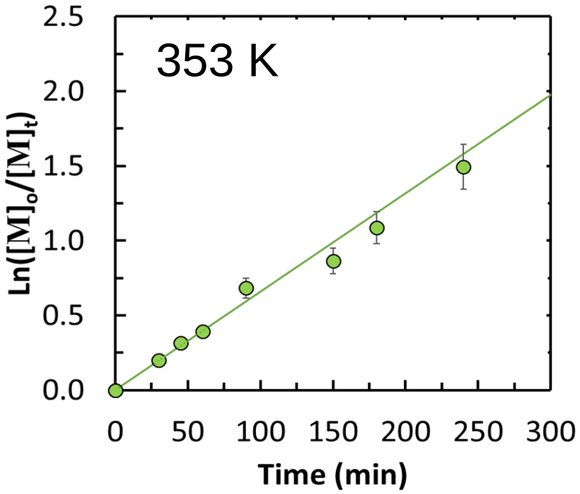


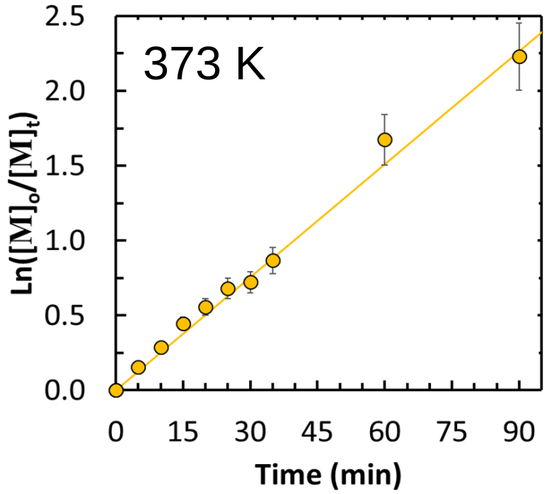


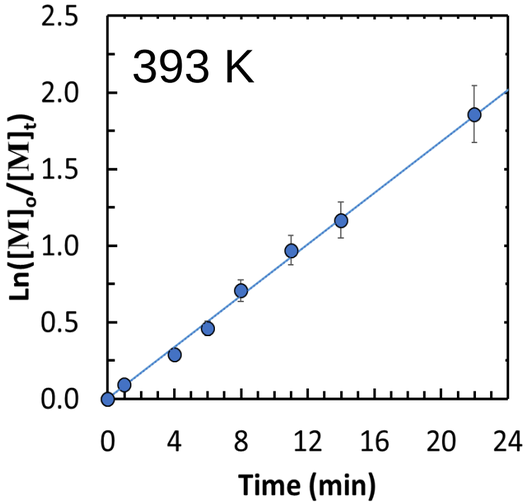


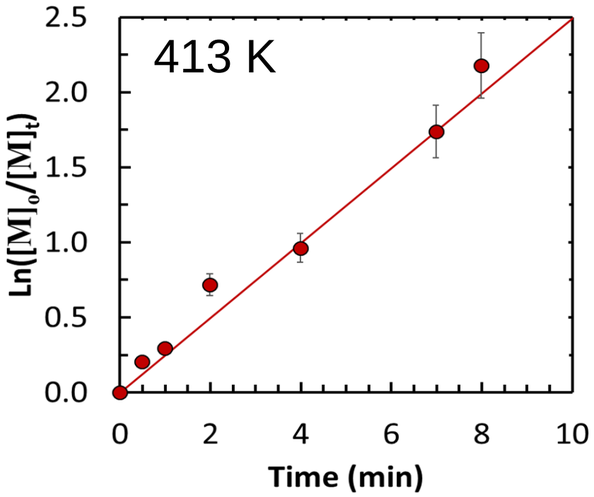
Absolute SEC traces accessible

SAME PROCEDURE (T) TO OBTAIN ARRHENIUS PARAMETERS

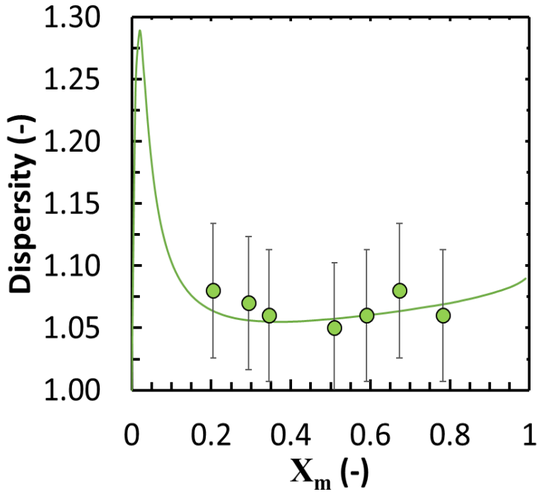


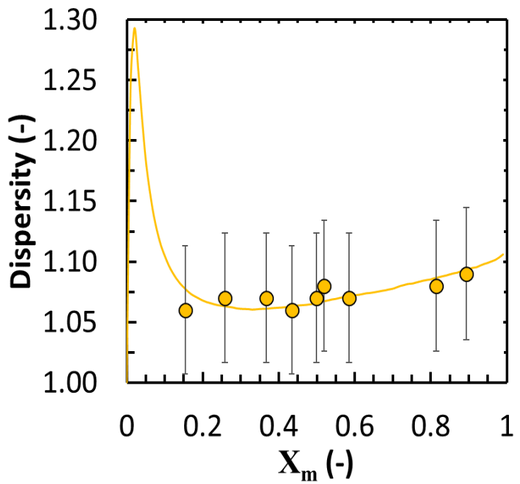


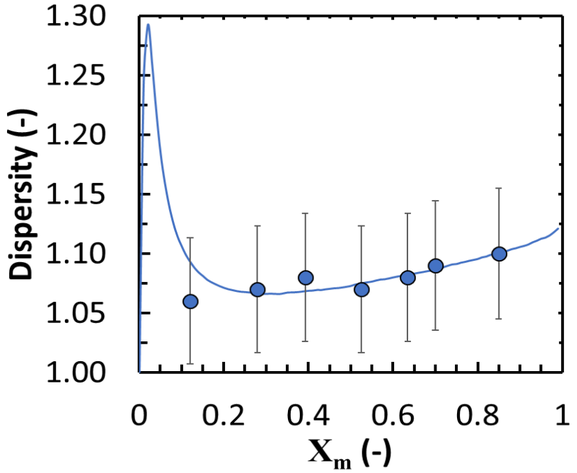


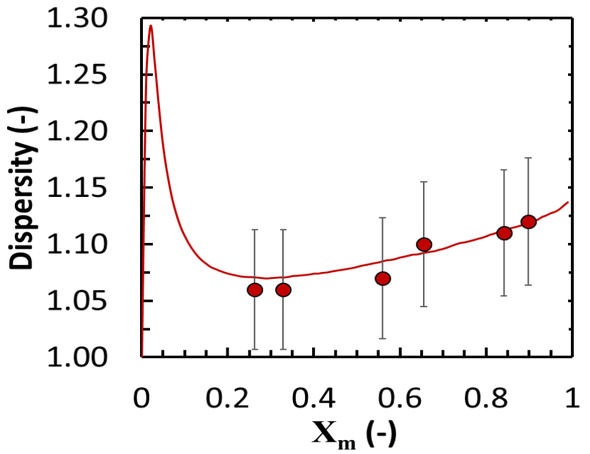


data from before

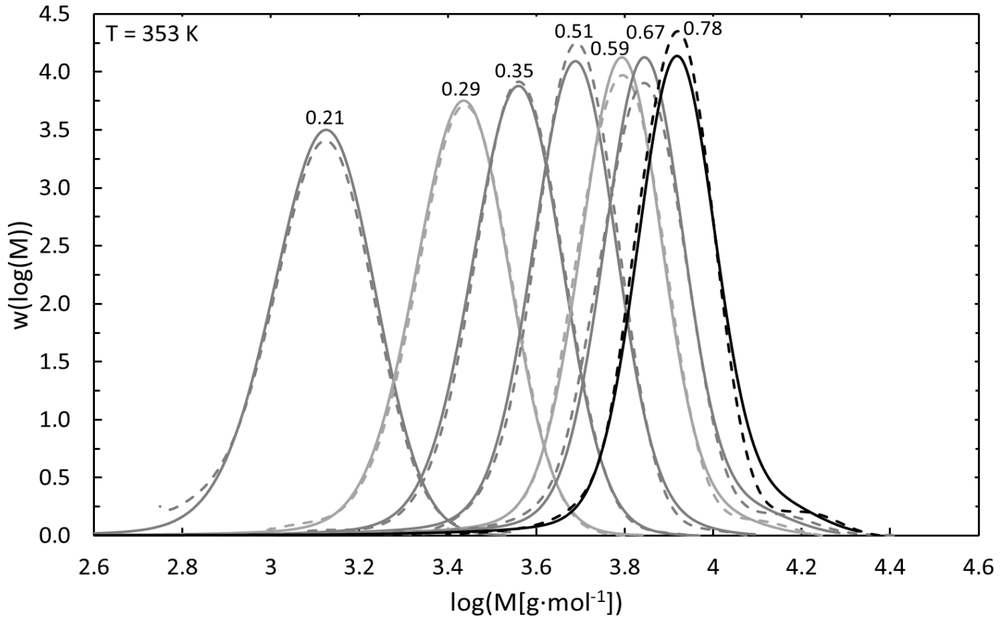


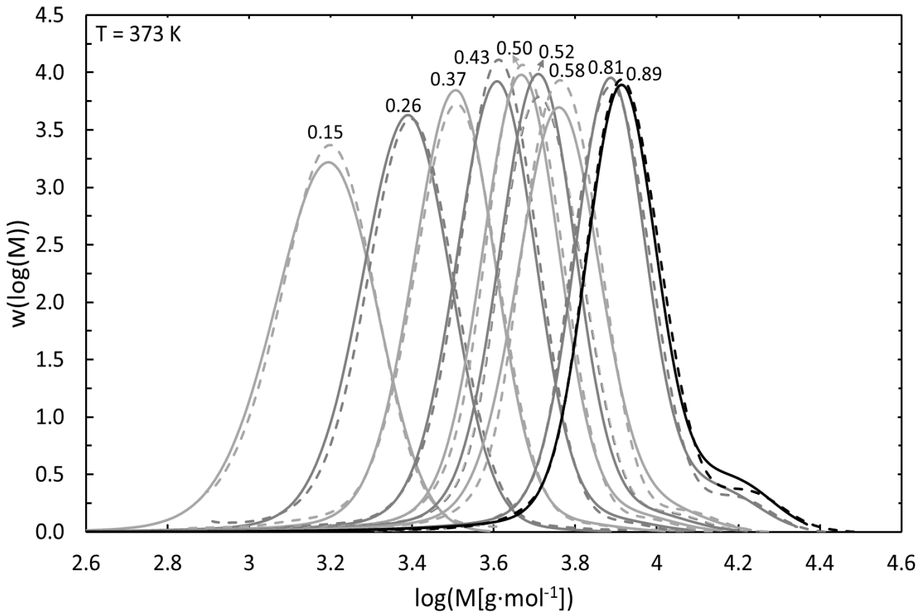


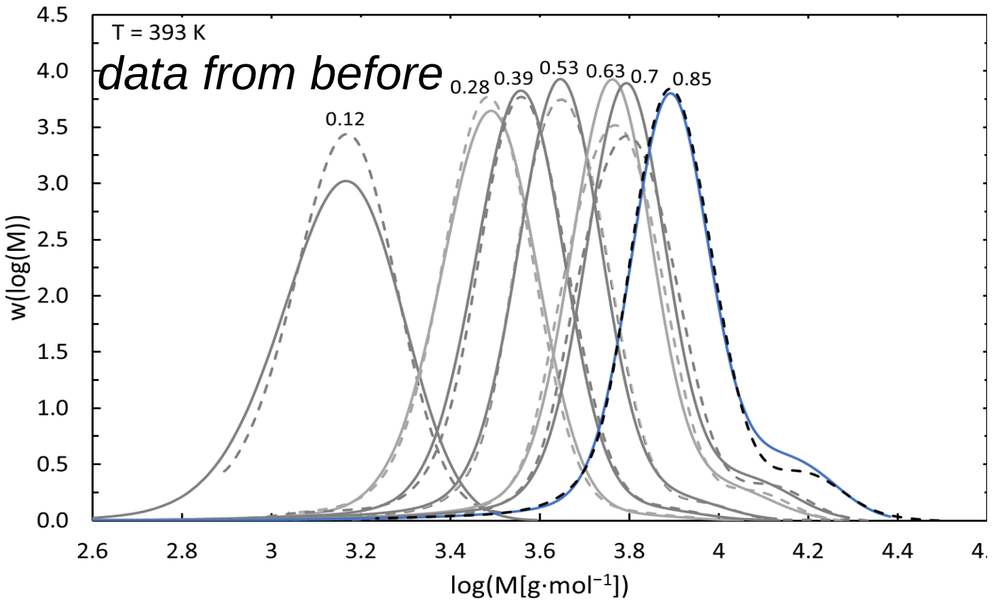


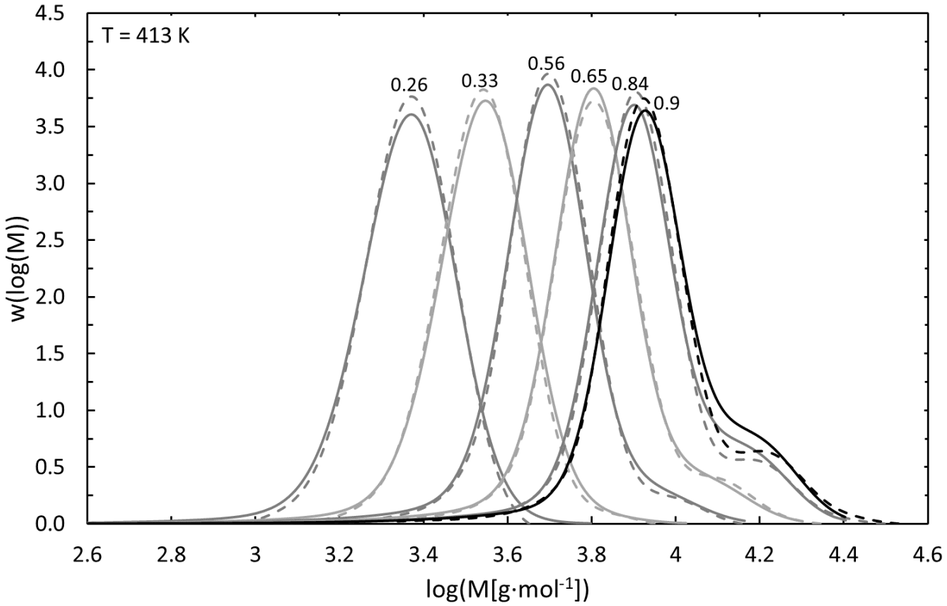


SAME PROCEDURE (T) TO OBTAIN ARRHENIUS PARAMETERS

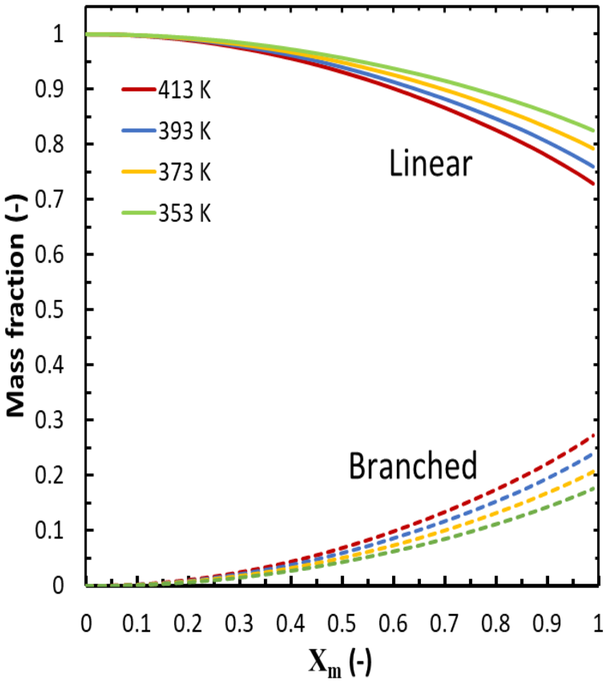






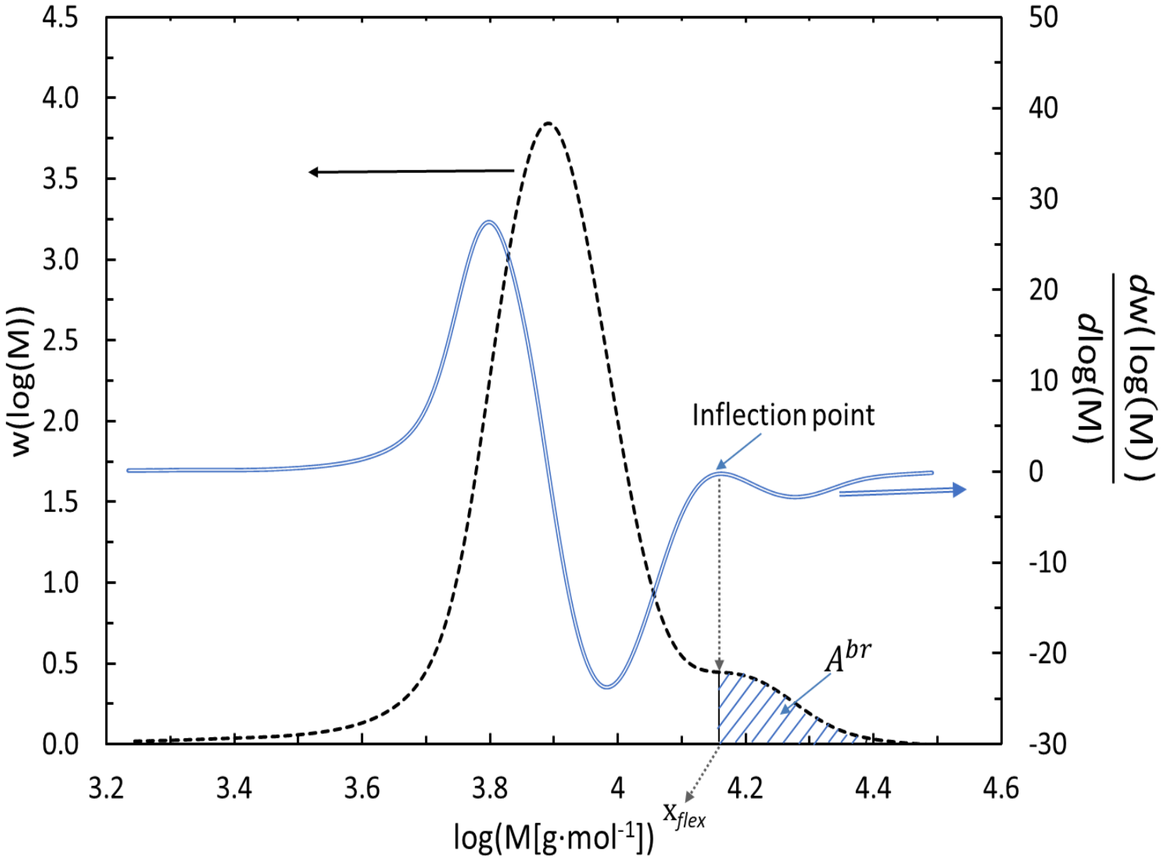


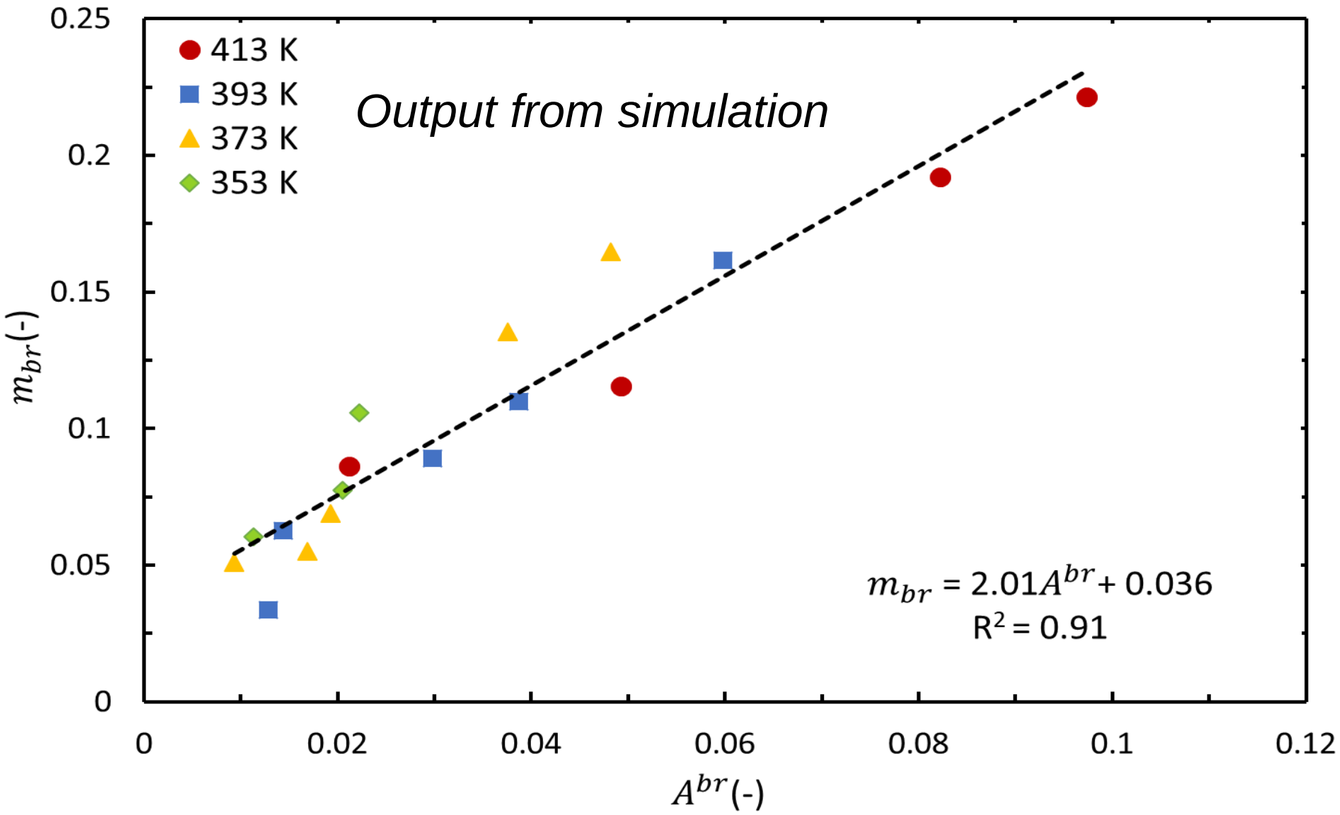
extra information by modeling



REVERSE ENGINEERING: DIRECT EXPERIMENTAL ANALYSIS ?

Linear calibration curve** to assess the **importance of branched species





Input from experimental SEC trace

OUTLINE

1. **Homopolymerization**
   - Chain initiation and propagation reactivity
   - Chain transfer to monomer reactivity
   - Macropropagation reactivity

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Glassner *et al. Eur. Polym. J.*, **2015**, 65, 298
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2. **Copolymerization with functional comonomer in view of therapeutics & hydrogels**
   - Unbiased qualification tool for evaluation functionalization success
   - Design of chemical structure of the comonomers and reaction conditions
   - Applicability for low and high target degrees of polymerization (target DPs)

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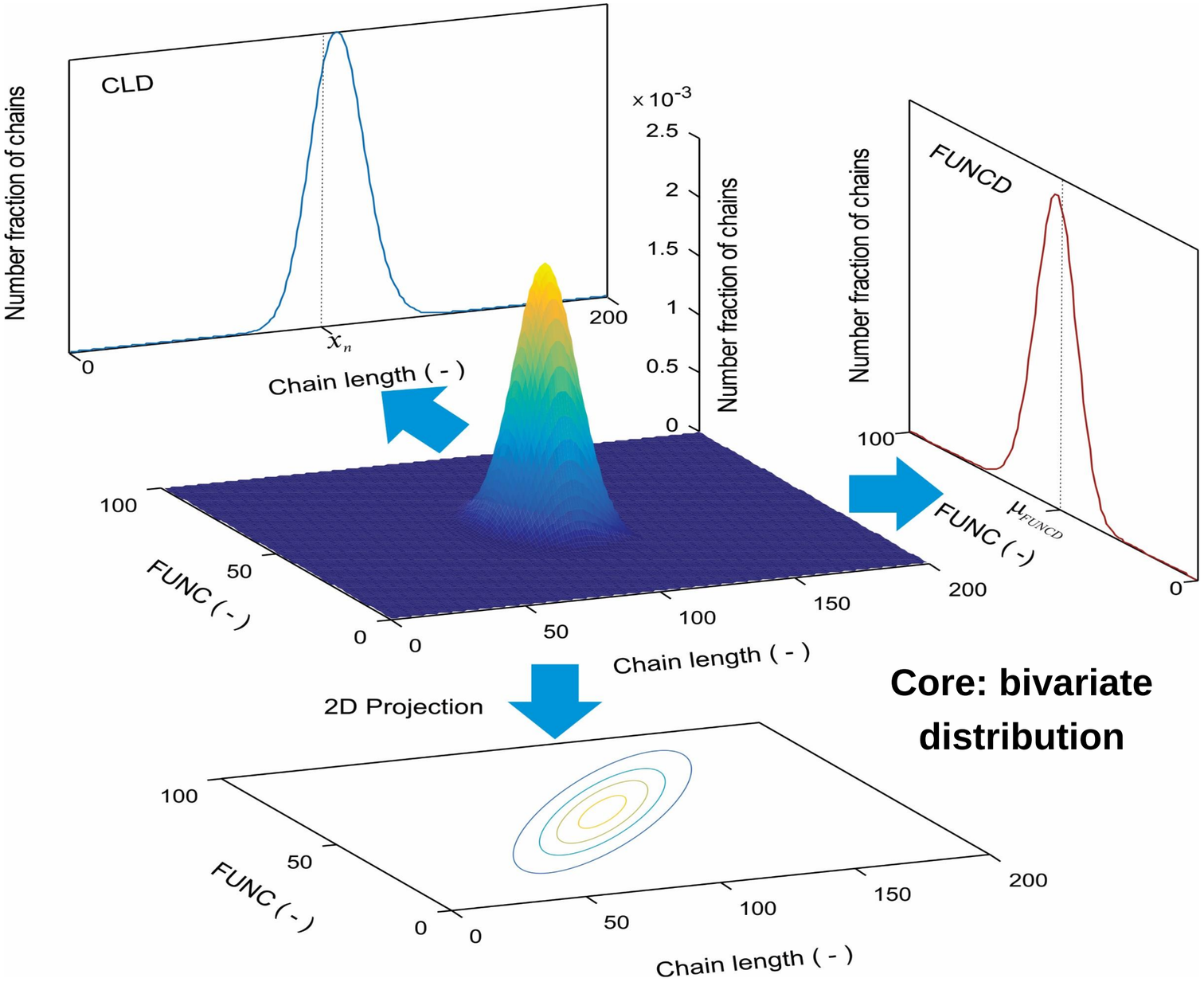
Van Steenberge *et al*. Submitted **2019**.

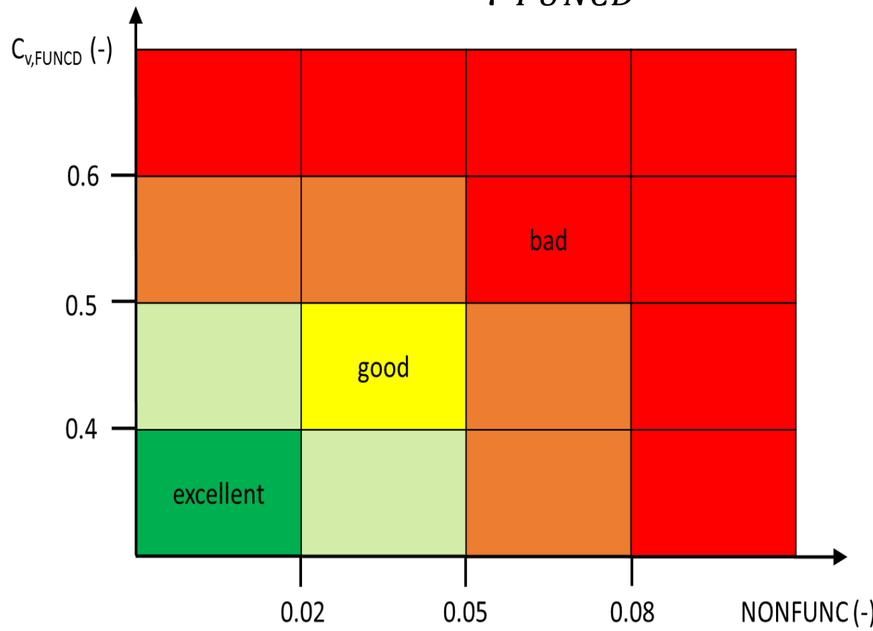
CONCEPT OF FUNCTIONALITY-CHAIN LENGTH DISTRIBUTION



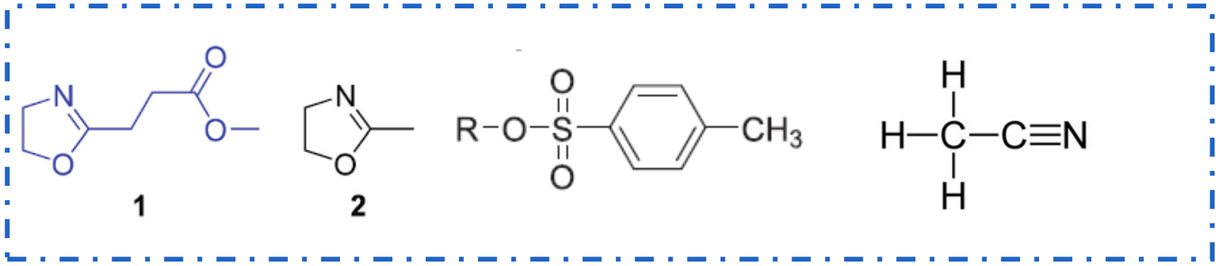
Core: bivariate distribution

derived properties

$$C_{v,FUNCD} = \frac{\sigma_{FUNCD}}{\mu_{FUNCD}}$$



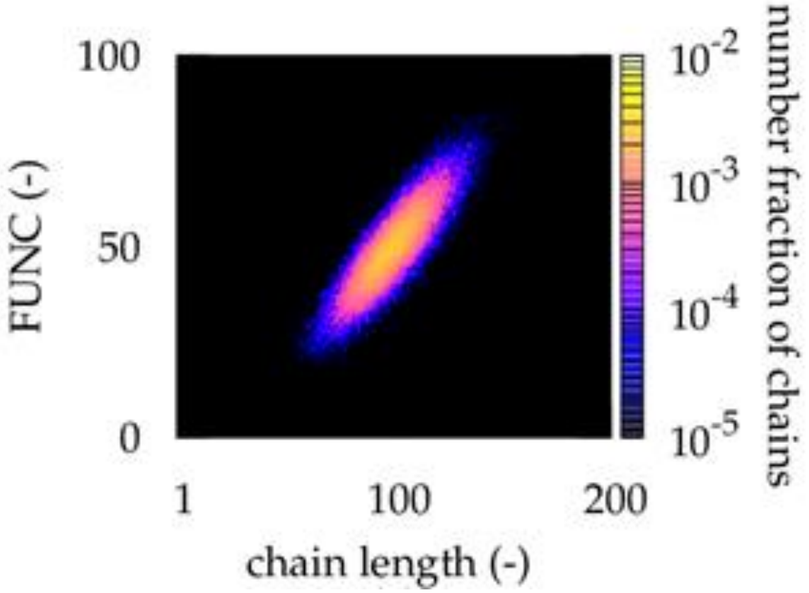
APPLICATION FOR CROP OF MEOX AND C2MESTOX: 1. EQUIMOLAR



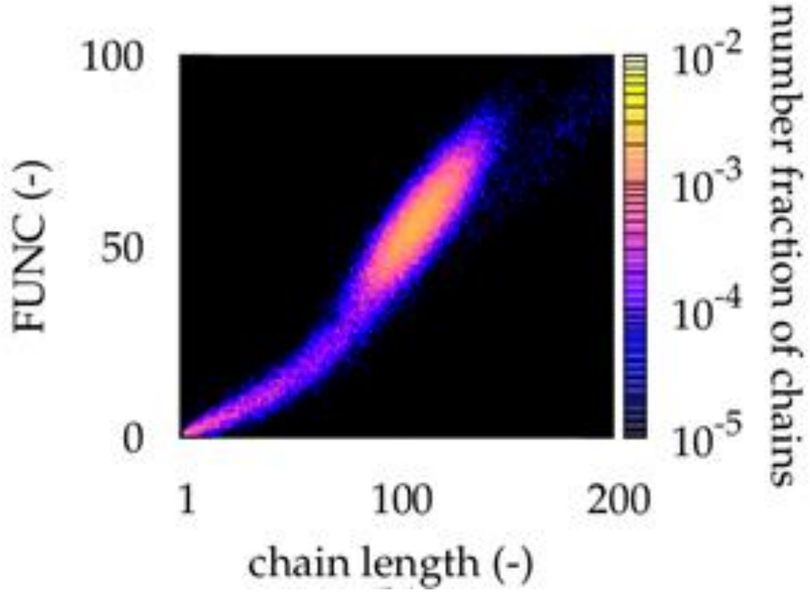
fingerprint of copolymer product quality

rate coefficients cf. first part

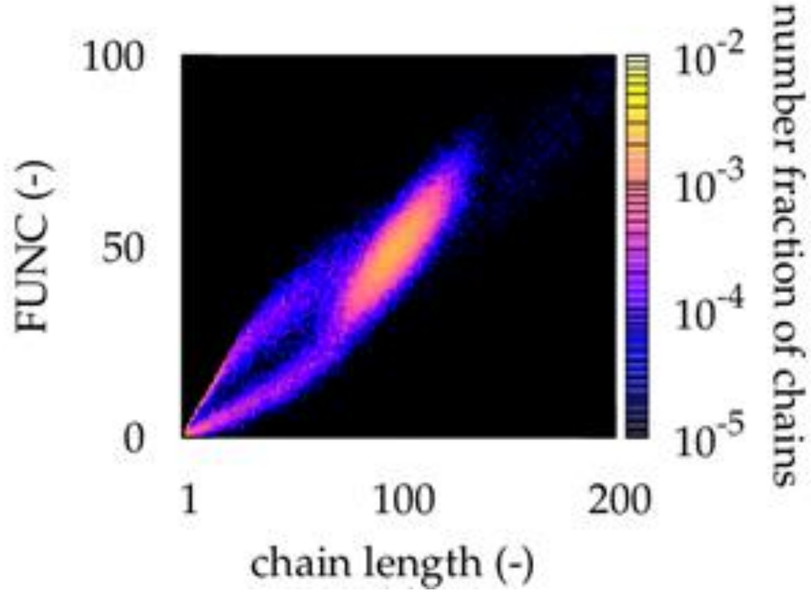
no side reactions



chain transfer to monomer

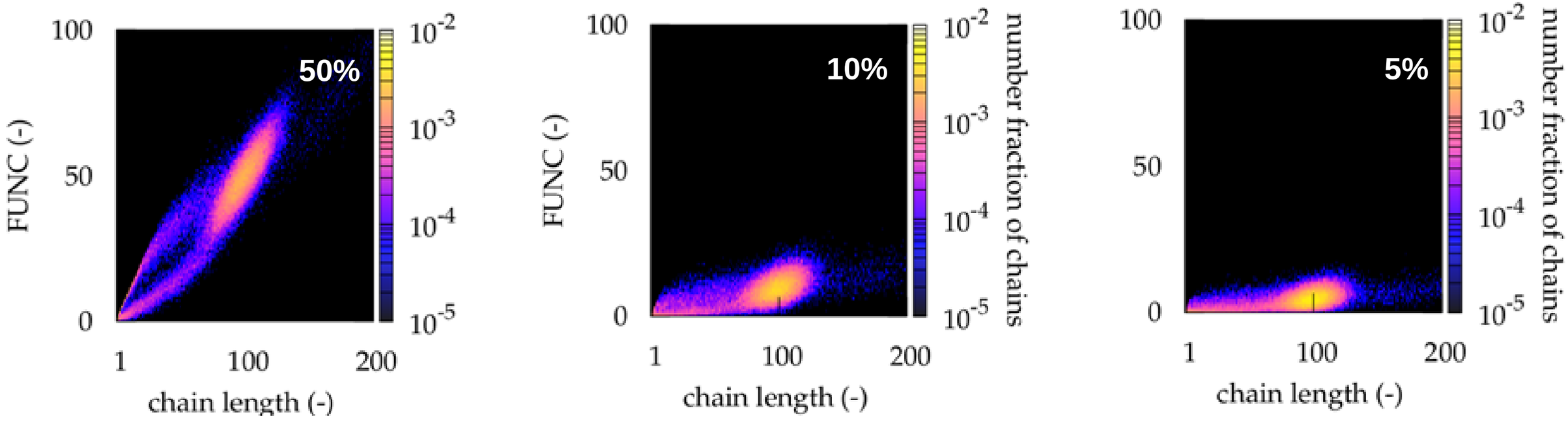


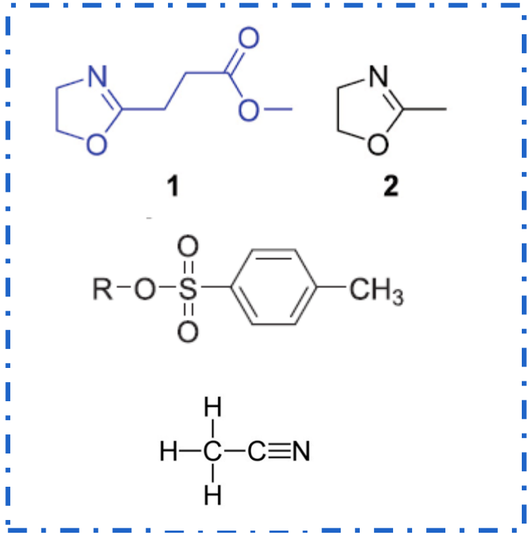
+ extra chain initiation & macropropagation

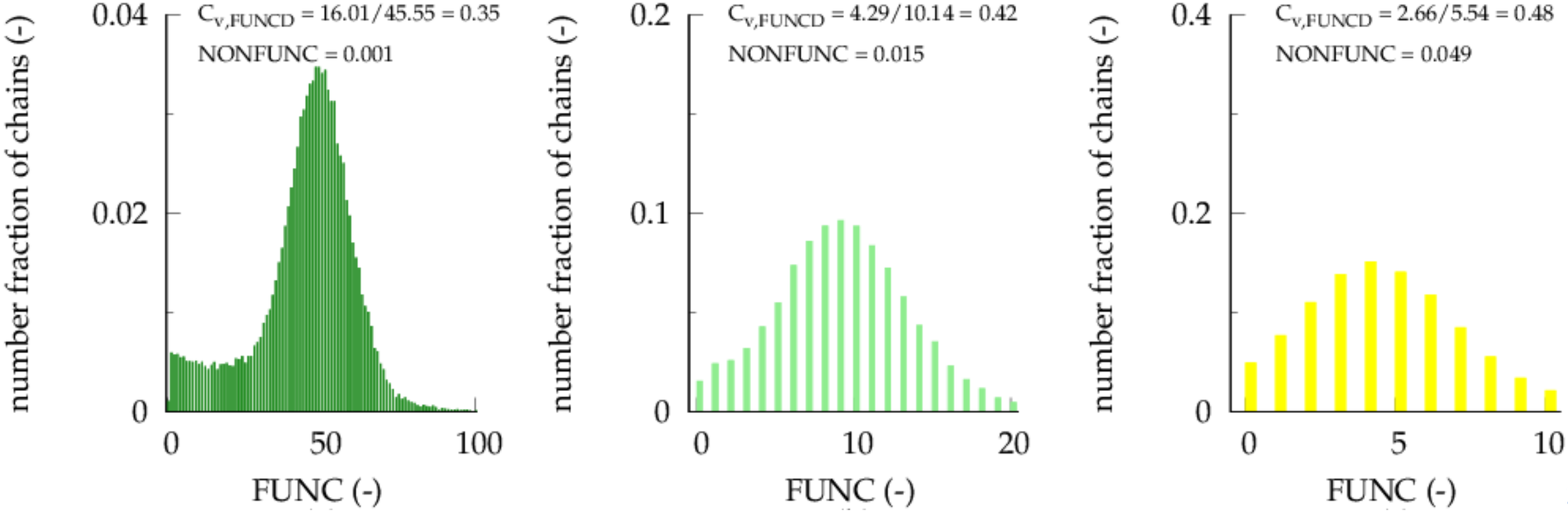


total monomer concentration: 3 mol L^{-1}; solvent acetonitrile; target DP of 100; 413 K; overall monomer conversion of 100%

APPLICATION FOR CROP OF MEOX AND C2MESTOX: 2. LOWER AMOUNTS

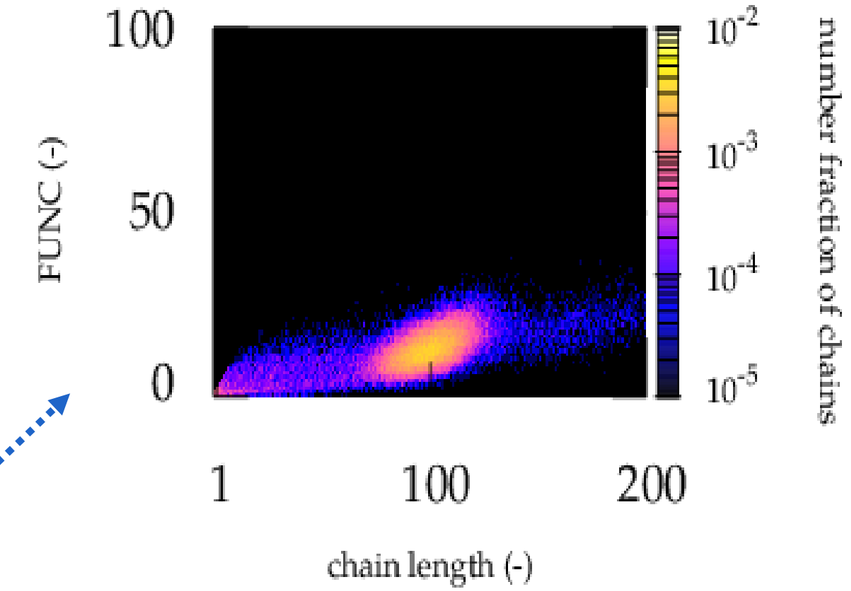


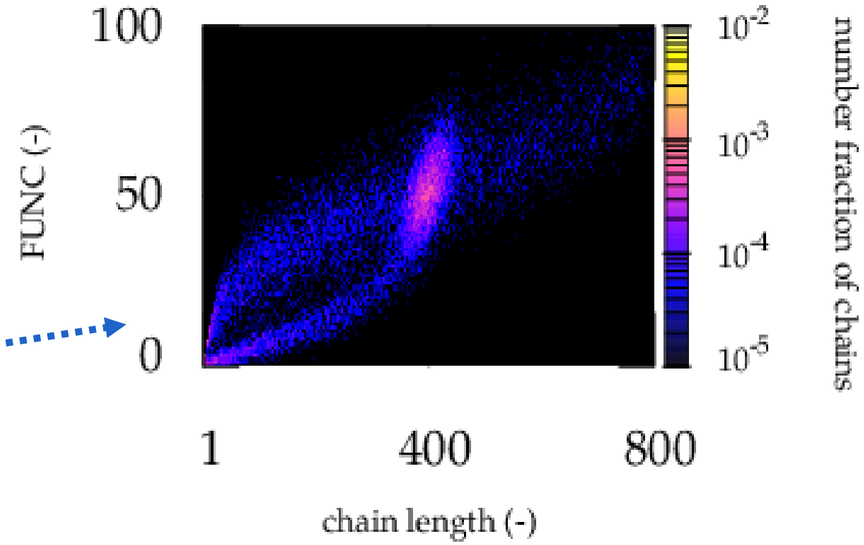




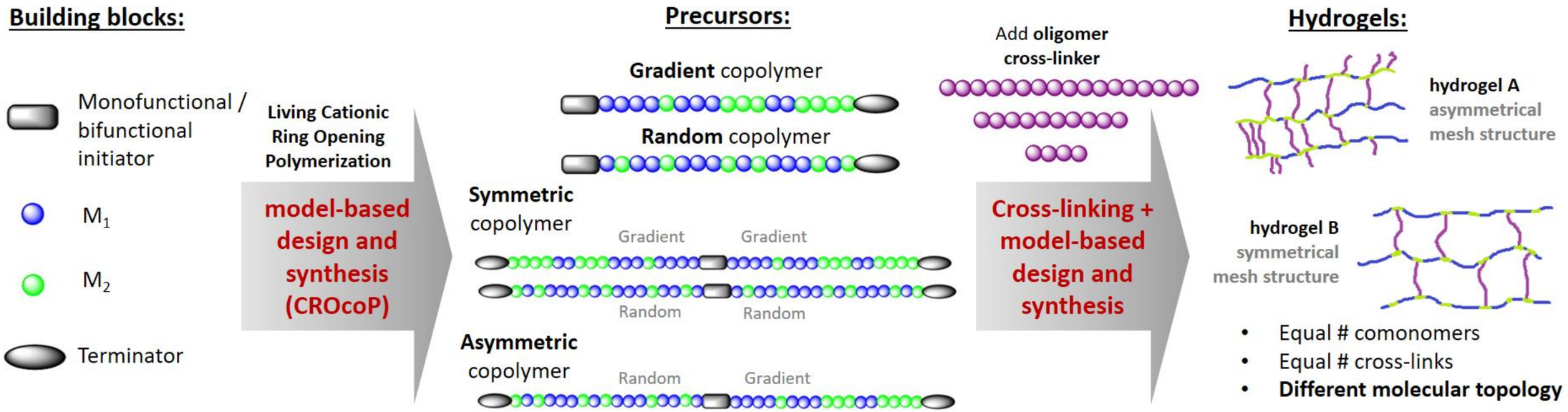
STRENGTH OF MODEL: DESIGN OF CROP PROCESS

	Reaction conditions	$C_{v,FUNCD}$ & NONFUNC (-)	
		MeOx/C2MestOx	EtOx/C2MestOx
1	$f_{C2Mest0x,0}$=0.02; target DP=100; T=100°C	0.527 & 0.195	0.522 & 0.213
2	$f_{C2Mest0x,0}$=0.02; target DP=100; T=140°C	0.531 & 0.205	0.539 & 0.238
3	$f_{C2Mest0x,0}$=0.02; target DP=400; T=100°C	0.554 & 0.072	0.627 & 0.106
4	$f_{C2Mest0x,0}$=0.02; target DP=400; T=140°C	0.602 & 0.101	0.677 & 0.137
5	$f_{C2Mest0x,0}$=0.10; target DP=100; T=100°C	0.415 & 0.012	0.413 & 0.019
6	$f_{C2Mest0x,0}$=0.10; target DP=100; T=140°C	0.424 & 0.015	0.447 & 0.026
7	$f_{C2Mest0x,0}$=0.10; target DP=400; T=100°C	0.497 & 0.011	0.599 & 0.014
8	$f_{C2Mest0x,0}$=0.10; target DP=400; T=140°C	0.564 & 0.018	0.672 & 0.021
9	**$f_{C2Mest0x,0}$=0.13; *target DP=100*; T=100°C**	**0.393 & 0.008**	0.396 & 0.011
10	$f_{C2Mest0x,0}$=0.13; target DP=100; T=140°C	0.411 & 0.012	0.432 & 0.016
11	**$f_{C2Mest0x,0}$=0.13; *target DP=400*; T=100°C**	**0.481 & 0.008**	0.593 & 0.009
12	$f_{C2Mest0x,0}$=0.13; target DP=400; T=140°C	0.561 & 0.013	0.664 & 0.013





FUTURE OUTLOOK



Kinetic Monte Carlo (kMC) simulation of molecular structure:

- Precursor (segment length, FUNC-CLD, …)
- Hydrogel (mesh size, mesh symmetry, …)

Design and synthesis of complex polymeric structures like hydrogels for various biomedical applications such as drug delivery, tissue engineering, among others.

CONCLUSIONS

1. Modeling & experimental work allow to understand CROP of 2-oxazolines
    - chain initiation reactivity: ln and low conversion dispersity data
    - chain transfer to M reactivity: high monomer conversion dispersity data
    - macropropagation reactivity: SEC trace data
    - access to absolute MMD data for all macrospecies types
    - simple method to assess branching fraction

2. The strength is more clear upon the transition to copolymerization with functional M
    - FUNC-CLD and derived properties allow for an unbiased qualification
    - after parameter tuning all experimental possibilities can be screened
    - optimal synthesis conditions can be identified for low and high target DPs

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